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Non-interventional 1-year follow-up study of peri-implant soft tissues following previous soft tissue augmentation and crown insertion in single-tooth gaps

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Abstract: AIM To assess peri-implant soft tissue dimensions at implant sites, previously augmented with a collagen matrix (VCMX) or an autogenous subepithelial connective tissue graft (SCTG), between crown insertion and 1 year. METHODS Twenty patients with single-tooth implants received soft tissue augmentation prior to abutment connection randomly using VCMX or SCTG. Following abutment connection 3 months later, final reconstructions were fabricated and inserted (baseline). Patients were recalled at 6 months (6M) and at 1 year (FU-1). Measurements included clinical data, soft tissue thickness, volumetric outcomes and patient-reported outcome measures (PROMs). RESULTS The buccal soft tissue thickness showed a median decrease of -0.5 mm (-1.0;0.3) (VCMX) and 0.0 mm (-0.5;1.0) (SCTG) (p = .243) up to FU-1. The soft tissue volume demonstrated a median decrease between BL and FU-1 of -0.1 mm (-0.2;0.0) (p = .301) for VCMX and a significant decrease of -0.2 mm (-0.4; -0.1) (p = .002) for SCTG, respectively. Intergroup comparisons did not reveal any significant differences between the groups for peri-implant soft tissue dimensions and changes up to FU-1 (p > .05). PROMs did not show any significant changes over time nor differences between the groups. CONCLUSION Between crown insertion and 1 year, the buccal peri-implant soft tissue dimensions remained stable without relevant differences between sites that had previously been grafted with VCMX or SCTG.

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Non-interventional 1-year follow-up study of peri-implant soft tissues following previous soft tissue augmentation and crown insertion in single tooth gaps

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Running title: volume stability of implant sites

Key words: soft tissue augmentation, soft tissue volume, collagen-based matrix, subepithelial connective tissue graft, dental implant, 1-year follow-up

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CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

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CLINICAL RELEVANCE

Scientific rationale for the study: For augmenting soft tissue volume around dental implants, autogenous subepithelial connective tissue grafts (SCTGs) and a recently developed three-dimensionally stable collagen matrix (VCMX) showed similar results in augmented volume up to 3 months. Longer-term data for VCMX are not available so far.

Principal findings: Between crown insertion and 1 year, the buccal soft tissue dimensions remained stable without relevant differences between sites that had previously been grafted with VCMX or SCTG.

Practical implications: Once, final reconstructions were inserted and up to 1 year, peri-implant soft tissues previously grafted with VCMX or SCTG remained stable.

ABSTRACT

Aim: To assess peri-implant soft tissue dimensions at implant sites, previously augmented with a collagen matrix (VCMX) or an autogenous subepithelial connective tissue graft (SCTG), between crown insertion and 1 year.

Methods: Twenty patients with single-tooth implants received soft tissue augmentation prior to abutment connection randomly using VCMX or SCTG. Following abutment connection 3 months later, final reconstructions were fabricated and inserted (baseline). Patients were recalled at 6 months (6M) and at 1 year (FU-1). Measurements included: clinical data, soft tissue thickness, volumetric outcomes and patient-reported outcome measures (PROMs).

Results: The buccal soft tissue thickness showed a median decrease of -0.5mm (-1.0;0.3) (VCMX) and 0.0mm (-0.5;1.0) (SCTG) (p=0.243) up to FU-1. The soft tissue volume demonstrated a median decrease between BL and FU-1 of -0.1mm (-0.2;0.0) (p=0.301) for VCMX and a significant decrease of -0.2mm (-0.4:-0.1) (p=0.002) for SCTG respectively. Intergroup comparisons did not reveal any significant differences between the groups for peri-implant soft tissue dimensions and changes up to FU-1 (p>0.05). PROMs did not show any significant changes over time nor differences between the groups.

Conclusion: Between crown insertion and 1 year, the buccal peri-implant soft tissue dimensions remained stable without relevant differences between sites that had previously been grafted with VCMX or SCTG.

INTRODUCTION

Peri-implant tissue health and stability over time are considered to be key factors in esthetic implant dentistry. Following tooth extraction, biological processes lead to a decrease in tissue volume, both, on the hard and soft tissue level (Araujo and Lindhe, 2005). Apart from applying various approaches to minimize these changes in ridge dimensions using ridge preservation procedures (Jung et al., 2017),missing tissue volume is usually regenerated applying bone augmentation procedures and/or soft tissue augmentation (Schneider et al., 2011) (Buser et al., 1990) (Eghbali et al., 2016)

More recently, clinical research focused on the relation between soft tissue quantity and quality and peri-implant tissue health. Based on systematic reviews and clinical studies, the soft tissue quality and quantity appear to play a crucial role in maintaining or improving peri-implant health over time (Akcali et al., 2016) (Gobbato et al., 2013).

Various techniques and materials were described in the literature to augment soft tissue volume, with the autogenous subepithelial connective tissue graft (SCTG) being considered the gold standard (Bassetti et al., 2016),(Thoma et al., 2014).

However, the use of autogenous soft tissue is associated with a number of disadvantages predominantly related to an increased patient morbidity and interindividual variations in terms of tissue quality and quantity that can be harvested (Burkhardt et al., 2015, Benninger et al., 2012). In order to overcome such limitations, a three-dimensionally stable collagen matrix (VCMX) was developed and subsequently evaluated in numerous preclinical and clinical studies, demonstrating favorable short-term results. (Thoma et al., 2010, Thoma et al., 2016, Zeltner et al., 2017).

While there is some evidence that pontic and implants sites, grafted with autogenous transplants maintain augmented tissue volume up to 10 years, similar data for soft tissue substitutes are lacking (Bienz et al., 2017b)

The aim of the present clinical study was, therefore, to assess peri-implant tissue health, stability and volume changes at implants sites, previously augmented with VCMX or SCTG, from the insertion of single-tooth reconstructions to 1 year.

Materials and Methods

Study design

The present investigation was designed as a follow-up study of patients earlier enrolled in a randomized controlled clinical trial and performed in accordance with the ISO Standard 14155:2011, Clinical Investigation of medical devices for human patients with the appendices VIII and X of the Medical Device Directive 93/42/EEC and with the Declaration of Helsinki, 2004 (Thoma et al., 2016). The study and its procedures were approved by the local ethics committee (KEK-ZH-Nr 2012-0226). The time-point 2 weeks following the insertion of the final reconstruction was considered as baseline (BL).

The following inclusion criteria were applied at baseline (BL) for the present follow-up study:

Inclusion criteria:

1. Patients previously enrolled into the previous RCT (Thoma et al., 2016) comparing augmented soft tissue volume by the use of an SCGT or VCMX (Geistlich Fibro-Gide® Geistlich Pharma AG, Wolhusen, Switzerland)
2. Final restoration inserted at implant site
3. Ability to fully understand the nature of the proposed non- interventional long-term follow-up study and the ability to sign the informed consent form

Exclusion criteria:

1. Newly developed disease interfering with soft tissue regeneration (e.g. diabetes)
2. Peri-implant infection (not related to previously performed soft tissue regeneration) following the insertion of the final reconstruction
3. Second soft tissue augmentation since completion of study (Thoma et al., 2016)
4. Severe trauma to implant site
5. Orthodontic treatment in the same quadrant

Clinical procedures

All participants were previously enrolled into a randomized controlled clinical trial (Thoma et al., 2016). In brief, 20 patients with a soft tissue volume deficiency after the placement of a single tooth implant were randomly allocated to receive a soft tissue augmentation using VCMX or SCTG. Three months after soft tissue grafting, abutment connection was performed and final reconstructions fabricated and inserted. The present study was then designed as a non-interventional study following the insertion of final reconstructions (all screw-retained, single-tooth crowns). Two weeks after the insertion of final reconstructions, baseline measurements were performed (BL) and patients re-examined at 6 months and 1 year.

Outcome measures

Assessment of soft tissue thickness

The primary outcome was the change in soft tissue thickness from BL to 12 months. The thickness of the mucosa was measured with an endodontic instrument (RS STER K-File 31/15, Dentsply Maillefer) 1mm apical of the margo mucosae at the mid-facial area of the implant-supported crown.

Assessment of the volumetric changes

At BL, 6 months (6M) and 1 year (FU-1), impressions of the implant sites were taken using an A-silicone impression material (Persident, Coltene /whaledent) including at least the two neighboring teeth and the respective mucosa. Dental stone casts were fabricated (Fujirock, Picodent) and optically scanned with a desktop 3D scanner (Imetric 3D, Courgenay, Switzerland). Subsequently, the obtained STL files were imported into a digital imaging software program (SMOP, Swissmeda, Zurich, Switzerland). A region of interest (ROI) was defined with a trapezoid shape. The ROI encompassed the following

borders: 1mm apical of the margo mucosae (coronal), the mucogingival junction (apical), 1mm distance from the neighboring tooth (mesial, distal). This ROI varied between patients, due to individual anatomical situations, but was kept constant in each patient and site over time. The images of the baseline and follow-up STLs were superimposed and matched using the best-fit algorithm at the adjacent tooth surfaces. The volumetric changes were calculated by the software measured in mm, which corresponded to the mean distance between the three surfaces representing the evaluated time-points (BL, 6M and FU-1).

Assessment of periodontal status

At BL, 6M and FU-1, standard clinical and periodontal measurements were performed at the implant sites and the two neighboring teeth: the plaque index (PlI), the width of keratinized tissue (KT) at the buccal aspect, bleeding on probing (BOP) and probing depth (PD).

Assessment of the soft tissue situation

The Pink Esthetic Score (PES) (Furhauser et al., 2005) was recorded at BL, 6M and FU-1, evaluating the soft tissues around the implants encompassing 7 parameters and scores from 0 (poorest) to 2 (best). The highest achievable score was 14.

Patient-reported outcome measures (PROMs)

At BL, 6M and FU-1, an oral health impact profile questionnaire (OHIP-G14) was filled out by the patients.

Statistical analysis

Mean, median, standard deviation and the quartiles Q1 and Q3 were used to describe the continuously scaled variables (expressed as median (Q1;Q3) lateron) and counts and percentages for categorically scaled variables. Nonparametric statistical methods were applied. The differences of the medians between the treatment groups were evaluated with the Mann-Whitney and within a treatment group with the Wilcoxon signed rank test. The treatment related differences of medians are expressed as Hodges-Lehmann-estimates incl. the 95%-confidence intervals.

The data were analyzed as intention-to-treat set (ITT: all randomized patients with post-baseline data). No relevant differences were found between the results in both analysis sets. The results for the primary objective are therefore presented as PP analysis set (ITT analysis is not generally conservative in non-inferiority trials).

As this was a follow-up investigation of a previous performed randomized controlled clinical trial, the sample size resulted out of the corresponding published study (Thoma et al., 2016)

RESULTS

All 20 patients originally included in the RCT entered the follow-up examination (baseline) between November 2012 and April 2015. Ten patients (mean age 44.1± 12.8 years) had been treated with a VCMX (7 female, 3 male) and 10 patients (mean age 43.4 ± 18.8 years) with a SCTG (6 female, 4 male). A detailed description on patient demographics and augmentation sites is displayed in Tables 1A and 1B. No relevant differences regarding baseline periodontal parameters were observed between the two groups. One patient in group VCMX was lost to follow-up after the baseline examination due to emigration. The remaining 19 patients attended all follow-up appointments and data were included in the analyses.

Soft tissue thickness

The median thickness of the mucosa at baseline was 3.0mm (3.0;4.0) (VCMX) and 3.0mm (2.5;3.0) (SCTG) (Hodges-Lehmann-estimation of difference: 0.5 [95%-CI: 0.0;1.0], p=0.128). Median changes from BL to FU-1 were minimal in both groups resulting in a final mucosal thickness of 3.0mm (2.0;3.0) (VCMX) and 2.8mm (2.0;4.0) (SCTG) at FU-1 (Hodges-Lehmann-estimation of difference: 0.0 [95%-CI: -1.0;1.0], p=0.900). The changes between the different time-points were not statistically significantly different within (p=0.231; p=0.563) and in between the groups (p=0.243). All data are displayed in Table 2.

Volumetric changes

The descriptive data for the volume changes between BL, 6M and FU-1 are presented in Table 3. Changes between BL and FU-1 demonstrated a median non-significant decrease in soft tissue volume of -0.1mm (-0.2;0.0) for VCMX (p=0.301) and a significant decrease of -0.2mm (-0.4;-0.1) for SCTG respectively (p=0.002). No statistically significant differences were observed between the two groups for these changes (Hodges-Lehmann-estimation of difference: 0.1 [95%-CI: -0.1;0.4], p=0.369)(Fig 1A and 1B).

Assessment of the soft tissue situation

At BL, median PES scores were 9.0 (9.0;11.0) for VCMX and 8.5 (6.0;11.0) for SCTG (p=0.444). The respective PES scores at FU-1 were 9.0 (8.0;10.0) for VCMX and 9.0 (7.0;11.0) for SCTG respectively (p=1.000). (Table 4) The PES score in the SCTG increased significantly up to 6 months with a median of 1.0 (0.0;3.0)(p=0.039) compared to a loss of -0.5 (-2.0;0.5)(p=0.406) for VCMX (intergroup comparison: p=0.031). From baseline to 1 year, PES scores remained stable in both group. The changes between the groups were not statistically significant (p=0.409).

Periodontal outcome measures

All implant sites demonstrated stable and healthy peri-implant tissues at BL, 6M and FU-1. No significant differences were observed between the groups for any of the outcome measures PlI, BOP and PD (p>0.05) (details see in Appendix Tables 1-3).

At BL, the keratinized tissue at the buccal aspect of the implant showed a median width of 2.0mm (2.0;3.0) (VCMX) and of 3.0mm (2.0;4.0) (SCTG) (p=0.293).

Both groups exhibited non-significant changes of the width of keratinized tissue over the observation time of 1 year (p=0.631), however resulting in a significant difference between the groups at 1 year (VCMX: 2.0mm (2.0;3.0); SCTG: 3.0mm (3.0;4.0) (p=0.037)) (Table 5).

Patient-reported outcome measures (PROMs)

Median overall OHIP scores were 0 at all time-points and in both groups (Table 6).

Discussion

The present non-interventional follow-up study demonstrated between the insertion of final reconstructions and one year of loading with single tooth reconstructions i) stable peri-implant soft tissue dimensions based on two- and three-dimensional analyses with minimal changes (<0.2mm) ii) healthy peri-implant tissues with minimal bleeding on probing and probing depth values; iii) stable esthetic outcomes based on PES scores in both groups.

The peri-implant tissues of the 19 included patients and sites demonstrated, over the course of 1 year following loading with final reconstructions, only minimal changes based on a two-dimensional (soft tissue thickness) analysis. The three-dimensional (buccal volume) analysis showed a significant volume decrease at the buccal aspect of the implant sites both at 6 months and at 1 year of follow-up in the autogenous group (SCTG). Meanwhile, the volume remained stable in the VCMX group. Encompassing, however, the entire observation period, no relevant differences and changes were observed between the two groups. Scientific evidence assessing changes of peri-implant tissues following the insertion of final reconstructions is limited. In a prospective case series, 16 patients and sites were followed for one year after loading with final reconstructions. During that observation period, a labial volume loss of 0.04±0.31mm was recorded (Schneider et al., 2011). The present study showed a slightly higher median volume loss of 0.1mm for VCMX and 0.2mm for SCTG. The study revealed a heterogeneous pattern of volume changes with a slight loss in an area closer to the mucosal margin and a slight gain in a more apical area. A high variability between patients and sites was observed, what could also be observed in the present investigation with a standard deviation of 0.5mm (VCMX) and 0.2mm (SCTG) after 1 year.

Longer-term data on volume changes of peri-implant tissues were reported by two recently published studies (Hanser and Khoury, 2016) (De Bruyckere et al., 2015).In a study reporting volume changes after implantation with a simultaneous connective tissue graft, 1 year after the insertion of the definitive implant-borne reconstructions, 50% of the reference points kept their volume from baseline to one year, whereas the other 50%

showed a significant decrease (Hanser and Khoury, 2016). Another prospective case series analyzed implant sites in the esthetic zone receiving a SCTG 3 months after implant placement. Mean soft tissue loss after 1 year was 0.10± 0.23mm with no difference between patients with a thin or thick biotype (De Bruyckere et al., 2015). These results are in accordance with the results of the present investigation, even though both studies used a slightly different method to analyze the changes of the peri-implant tissues.

More recently, the same method was used to evaluate volume changes of implant sites (Bienz et al., 2017a). Subepithelial connective tissue grafts were transplanted 3 months after implant placement. A median loss of -0.38mm was observed at the buccal aspect 5 years after placement of the definitive reconstruction. In that study, however, abutment connection was performed 4-6 weeks after the soft tissue augmentation. Compared to the present study protocol, the earlier loading of the peri-implant soft tissues could have led to a slightly better tissue volume stability.

Soft tissues undery changes beginning with the integration of the grafting material. Major changes can be expected up to the first 6 weeks after grafting (Studer et al., 2000),(Rotenberg and Tatakis, 2014). In the present study, the insertion of the final reconstruction was considered as baseline. All patients were then followed-up for one more year. Therefore, soft tissue grafting procedures had been performed at least 4 months earlier. Volume changes based on the initial grafting and healing period (3 months) were reported previously (Thoma et al., 2016). One could therefore speculate that at the baseline time-point of the present non-interventional follow-up study, maturation of the augmented sites had already taken place. This would then explain rather stable peri-implant contour dimensions between the insertion of the final reconstruction and the 1-year follow-up.

Apart from more favorable esthetics, data in the literature are controversial in terms of potential benefits on the health of the peri-implant tissues following soft tissue grafting procedures. Studies have shown, though, that in case of implant sites with peri-implant disease, soft tissue grafting using SCTGs results in an improved peri-implant health

(Schwarz et al., 2014a, Schwarz et al., 2015, Schwarz et al., 2014b). At implant sites with healthy peri-implant tissues, soft tissue grafting demonstrated to be beneficial with significantly less marginal bone loss (Thoma et al., 2017). In the present study, marginal bone level changes were not assessed, clinical indices for PD, PlI and BOP, however, were recorded. None of the assessed clinical parameters demonstrated any significant differences between the two groups, nor any significant changes over the 1-year observation period. These outcomes revealed that both treatment modalities rendered healthy peri-implant tissue.

Achieving a favorable esthetic result is often a challenge for clinicians. Soft tissue grafting can be beneficial for implant sites regarding the esthetic result (Cornelini et al., 2008, Rungcharassaeng et al., 2012). In order to assess the esthetic outcome of implant sites, numerous scoring systems and indices are available (Benic et al., 2012) (Cosyn et al., 2017) Among the most frequently used indices, is the so-called pink esthetic score (PES) (Furhauser et al., 2005). In the present study, both treatment groups achieved stable esthetic results based on median PES scores of 9.0 (VCMX) and 8.5 (SCGT) at baseline and 9.0 (VCMX) and 9.0 (SCTG) 1 year after loading. These results can also be explained by the case selection made in the present study. Every implant site was a single-tooth gap surrounded by natural teeth, presenting rather favorable conditions with the periodontium supporting the tissues of the adjacent implant. Moreover, the treatment protocol of the grafting procedure followed a delayed approach, at least 8 weeks after implant placement. In combination with a primary wound closure, the best possible blood supply was provided the grafts and the healing wound. Abutment connection was performed 3 months after the grafting, followed by the fabrication of the definitive implant-supported reconstruction. This protocol allowed for a further maturation of the peri-implant tissues before the insertion of the reconstruction, thereby explaining stable esthetic during the 1-year follow-up.

Conclusion

Between crown insertion and 1 year, the buccal peri-implant soft tissue dimensions at implant sites revealed only minimal changes without relevant differences between sites that had previously been grafted with VCMX or SCTG. Periodontal parameters remained stable over time and both treatment options resulted in esthetically stable results over the entire observation time.

Table and figure legends

Table 1A: Patient demographics and p-values (MWU-test). SD=standard deviation. Q1=25th percentile. Q3=75th percentile. VCMX=volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts.

Table 1B: Location and number of augmented sites for each group. VCMX=volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts.

Table 2: Soft tissue thickness and p-values (MWU-test) and change in soft tissue thickness and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. Diff. [95%-CI] : Hodges-Lehmann-estimate of the treatment related difference incl. 95%-confidence interval. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Table 3: Change in soft tissue volume and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. Diff. [95%-CI] : Hodges-Lehmann-estimate of the treatment related difference incl. 95%-confidence interval. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Table 4: Pink esthetic score and p-values (MWU-test) and change of pink esthetic score and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Table 5: Width of keratinized tissue and p-values (MWU-test) and change of width of keratinized tissue and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Table 6: OHIP-G14 score and p-values (MWU-test) SD=standard deviation. Q1=first quartile. Q3=third quartile. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Figure 1A: A case of the VCMX –group: A) Clincal situation at baseline of the implant born reconstruction 21 B) Clinical situation at 1 year follow-up C) Cross-section through superimposed STL-Files. Green line=Baseline STL. Red line=Follow-up at 1 year STL. MG=Margo Gingivae. ROI=Region of interest.

Figure 1B: A case of the SCTG–group: A) Clincal situation at baseline of the implant born reconstruction 12 B) Clinical situation at 1 year follow-up C) Cross-section through superimposed STL-Files. Green line=Baseline STL. Red line=Follow-up at 1 year STL. MG=Margo Gingivae. ROI=Region of interest.

Appendix legends

Appendix Table 1: Bleeding on probing and p-values (MWU-test) and change of bleeding on probing and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Appendix Table 2: Plaque-Index and p-values (MWU-test) and change of Plaque-Index and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

Appendix Table 3: Pocket depth and p-values (MWU-test) and change of Pocket depth and p-values (MWU-test). SD=standard deviation. Q1=first quartile. Q3=third quartile. VCMX= volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. BL=baseline. 6M=Follow-up at 6 months. FU-1=Follow-up at 1 year

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Table 1A

		VCMX	SCTG	p-value
Gender	n (female) n (male)	7 3	6 4	p=1.000
Age	Mean ± SD Median Q1;Q3	44.1 ± 12.8 46.0 39.0;48.0	43.4 ± 18.7 47.5 23.0;60.0	p=1.00
Cigarettes per day	Mean ± SD Median Q1;Q3	0.0 ± 0.0 0.0 0.0;0.0	1.0 ± 2.5 0.0 0.0;0.0	p=0.184

Table 1B

Site	15	14	13	12	11	21	22	23	24	25
VCMX	1				3	2			1	3
SCTG				2	2	4	1			

Site	45	44	43	42	41	31	32	33	34	35
VCMX										
SCTG						1				

Table 2

		VCMX [mm]	SCTG [mm]	p-value
BL	n Mean ± SD Median Q1;Q3 Diff. [95%-CI]	9 3.2 ± 0.8 3.0 3.0;4.0 0.5 [0.1;1.1]	10 2.7 ± 0.4 3.0 2.5;3.0	p=0.128
6M	N Mean ± SD Median Q1;Q3 Diff. [95%-CI]	8 2.9 ± 0.9 3.0 2.0;3.8 0.0 [-1.0;1.0]	10 3.0 ± 0.9 3.0 2.0;3.5	p=1.000
FU-1	n Mean ± SD Median Q1;Q3 Diff. [95%-CI]	9 2.8 ± 0.7 3.0 2.0;3.0 0.0 [-1.0;1.0]	10 3.1 ± 1.3 2.8 2.0;4.0	p=0.900
BL to 6M	n Mean ± SD Median Q1;Q3 p (within grp) Diff. [95%-CI]	8 -0.3 ± 0.9 0.0 -0.5;0.0 0.750 -0.3 [-1.0;0.0]	10 0.3 ± 1.0 0.0 0.0;1.0 0.500	p=0.318
BL to FU-1	n Mean ± SD Median Q1;Q3 p (within grp) Diff. [95%-CI]	8 -0.4 ± 0.9 -0.5 -1.0;0.3 0.231 -0.5 [-2.0;0.5]	10 0.4 ± 1.4 0.0 -0.5;1.0 0.563	p=0.243

Table 3

		VCMX [mm]	SCTG [mm]	p-value
BL to 6M	n	9	10	p=0.462
	Mean ± SD	-0.1 ± 0.4	-0.2 ± 0.2	
	Median	0.0	-0.1	
	Q1;Q3	-0.2;0.1	-0.3;0.0	
	p (within grp)	0.574	**0.049**	
	Diff. [95%-CI]	0.1 [-0.2;0.3]		
BL to FU-1	n	9	10	p=0.369
	Mean ± SD	-0.2 ± 0.5	-0.2 ± 0.2	
	Median	-0.1	-0.2	
	Q1;Q3	-0.2;0.0	-0.4;-0.1	
	p (within grp)	0.301	**0.002**	
	Diff. [95%-CI]	0.1 [-0.1;0.4]		

Table 4

		VCMX	SCTG	p-value
BL	n	10	10	p=0.444
	Mean ± SD	9.6 ± 1.6	8.4 ± 3.5	
	Median	9.0	8.5	
	Q1;Q3	9.0;11.0	6.0;11.0	
6M	n	8	10	p=0.302
	Mean ± SD	8.8 ± 1.8	9.8 ± 3.3	
	Median	9.0	10.0	
	Q1;Q3	7.5;9.5	7.0;12.0	
FU-1	n	9	10	p=1.000
	Mean ± SD	8.9 ± 2.4	9.1 ± 2.1	
	Median	9.0	9.0	
	Q1;Q3	8.0;10.0	7.0;11.0	
BL to 6M	n	8	10	**p=0.031**
	Mean ± SD	-0.6 ± 1.7	1.4 ± 1.6	
	Median	-0.5	1.0	
	Q1;Q3	-2.0;0.5	0.0;3.0	
	p (within grp)	0.406	**0.039**	
BL to FU-1	n	9	10	p=0.409
	Mean ± SD	-0.4 ± 2.7	0.7 ± 1.9	
	Median	-1.0	1.0	
	Q1;Q3	-2.0;2.0	-1.0;2.0	
	p (within grp)	0.789	0.305	

Table 5

		VCMX [mm]	SCTG [mm]	p-value
BL	n Mean ± SD Median Q1;Q3	10 2.5 ± 0.8 2.0 2.0;3.0	10 3.2 ± 1.4 3.0 2.0;4.0	p=0.293
6M	n Mean ± SD Median Q1;Q3	9 2.7 ± 1.2 2.5 2.0;3.0	10 3.1 ± 0.9 3.0 2.0;4.0	p=0.333
FU-1	n Mean ± SD Median Q1;Q3	9 2.1 ± 1.2 2.0 2.0;3.0	10 3.2 ± 0.8 3.0 3.0;4.0	**p=0.037**
BL to 6M	n Mean ± SD Median Q1;Q3 P (within grp)	9 0.3 ± 0.9 0.0 0.0;1.0 0.406	10 -0.1 ± 1.3 0.0 0.0;0.0 1.000	p=0.516
BL to FU-1	n Mean ± SD Median Q1;Q3 P (within grp)	9 -0.2 ± 0.7 0.0 -1.0;0.0 0.625	10 0.0 ± 1.2 0.0 -1.0;1.0 1.000	p=0.631

Table 6

		VCMX	SCTG	p-value
BL	n Mean ± SD Median Q1;Q3	10 2.1 ± 5.0 0.0 0.0;1.0	10 0.6 ± 1.3 0.0 0.0;1.0	p=0.624
6M	n Mean ± SD Median Q1;Q3	8 1.3 ± 3.2 0.0 0.0 ;0.5	10 0.4 ± 1.3 0.0 0.0;0.0	p=0.452
FU-1	n Mean ± SD Median Q1;Q3	9 1.0 ± 2.6 0.0 0.0;0.0	10 0.5 ± 1.6 0.0 0.0;0.0	p=0.520

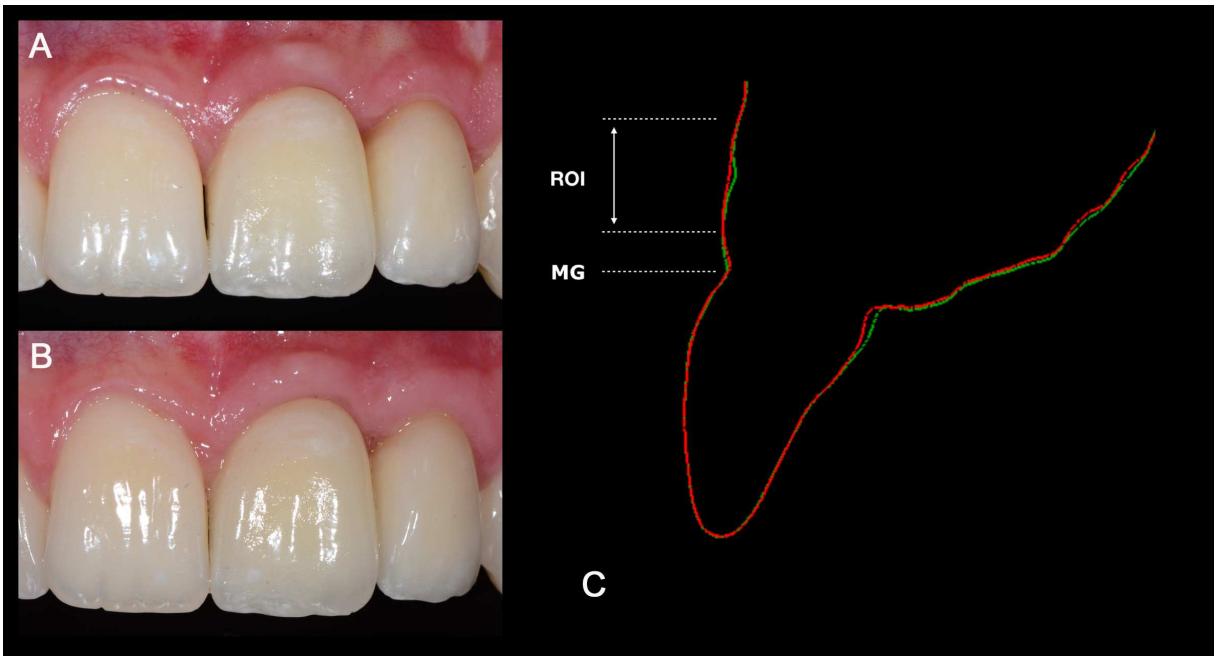

Figure 1a

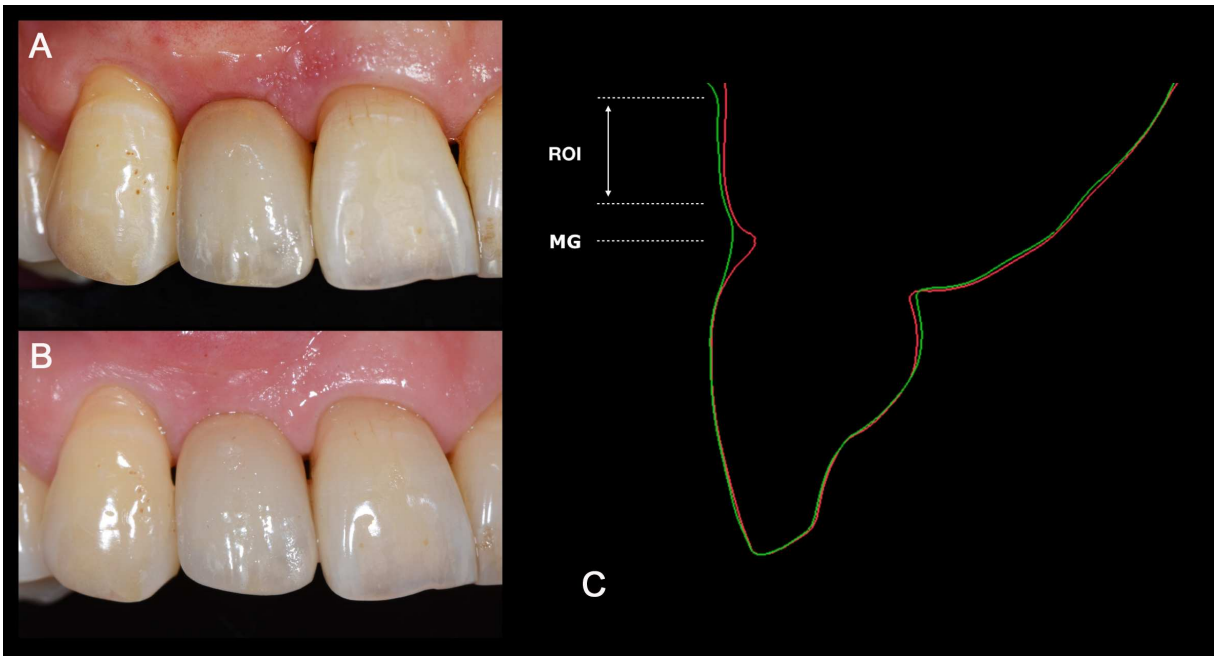

Figure 1b